Specialty Conference

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Gallstones

Cholesterol saturation of bile has a primary role in the pathogenesis of gallstone formation. Predisposing factors should be considered. The characteristic features of biliary colic are important to keep in mind, as well as the fact that a history of fatty food intolerance is not of value in the diagnosis of gallstones. The technique of endoscopic retrograde cholangiography is useful for the diagnosis of bile duct stones in jaundiced patients and in patients with a strong clinical history, but in whom findings on oral and intravenous cholangiograms are within normal limits. Improved techniques of operative cholangiography to diminish the incidence of retained gallstones have been developed. Also, choledochoscopy provides a remarkable technique for diagnosis and choledocholithotomy. The dissolution of gallstones with chenodeoxycholic acid is an experimental procedure. This bile acid is thought to act by increasing the chenodeoxycholic acid pool size and decreasing cholesterol synthesis and secretion, thereby reversing the defects responsible for gallstone formation.

LESLIE J. SCHOENFIELD, MD, PH D:* The purpose of this conference is to discuss recent advances in the pathogenesis, diagnosis and management of gallstones. Dr. Leonard Goldstein will review the mechanism of gallstone formation, risk factors for the development of gallstones and selected clinical features. Dr. Joel Panish will describe the diagnostic and therapeutic use of endoscopic retrograde cholangiography. Dr. J. Manny Shore will discuss advances in operative cholangiography for the prevention of retained gallstones, as well as advances in choledochoscopy for the operative diagnosis of ductal stones and choledocholithotomy. Finally, I will present the current status of the efficacy, adverse effects and mechanism of action of chenodeoxycholic acid in the medical dissolution of gallstones.

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CLINICAL ASPECTS OF GALLSTONE DISEASE

LEONARD I. GOLDSTEIN, MD:† The occurrence of gallstones, Ingelfinger noted a few years ago, has not been an "in disease" and has been "grossly neglected by the medical profession."[1] This situation is now changing; research advances in the pathogenesis of cholesterol gallstones have brought us to the threshold of a new era, promising both prophylaxis and medical treatment. The need for such therapy is emphasized by the prevalence of gall-

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stones in the United States. Keeping in mind the "iceberg phenomenon" of asymptomatic stones, gallstones occur in approximately 16 to 20 million Americans (10 percent of men and 20 percent of women in the 55 to 64 age group). They develop in about 1 million people each year. In more than a third of a million persons annually, cholecystectomy is carried out, with 8,000 patients dying from complications of cholelithiasis and the operation each year. In women, cholecystectomy is a more common operation than appendectomy.[2] The cost of cholecystectomy and related problems is more than a billion dollars each year.

Types of Gallstones

The pathogenesis of gallstones and the potential for their dissolution by medical means depends on the type of gallstone. Mixed cholesterol stones account for about 80 percent of all stones analyzed in the United States.[3] These contain at least 70 percent cholesterol and, in addition, bile pigment, bile acids, calcium salts and a protein matrix. Such stones (seldom larger than 2 cm) may be either multiple, round or faceted as a result of pressure of adjacent stones. If these stones contain enough calcium, they may be radiopaque. Pigment stones (less than 10 percent of all stones) are composed of bile pigment, calcium and a matrix of organic material. These calculi are usually multiple, small, dark-colored, irregular, hard and glistening; about 10 percent are radiopaque. Pigment stones are found in patients with chronic hemolysis,[4] in Orientals with parasitic infections and in patients having biliary obstruction and infection, especially with Escherichia coli.[5] In this review, we shall concentrate on cholesterol gallstones, their pathogenesis and clinical associations.

States of Cholesterol Gallstone Formation

Cholesterol gallstone formation may be divided into three stages: saturation, crystallization and growth.[6]

- *Saturation*

This critical stage involves alteration of the biliary lipid proportions, resulting in an abnormal bile saturated with cholesterol. Bile that is saturated or contains excess cholesterol relative to the other biliary lipids is prerequisite to gallstone formation and has been termed lithogenic.[7,8] Supersaturated bile is thermodynamically unstable

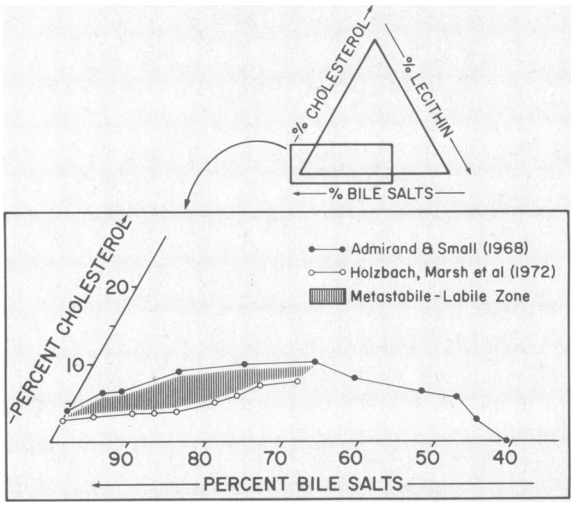

Figure 1.—Biliary lipid composition of bile expressed on triangular coordinates. Points below the metastable-labile zone indicate unsaturated bile. The zone defines supersaturated bile as metastable when nucleation of cholesterol is slow (lower limit of zone), and labile when it is rapid (upper limit). Above the zone, cholesterol is in a crystalline or liquid crystalline phase. (Courtesy of Dr. Martin D. Carey.)

and may precipitate. It has the potential for, but does not always result in, gallstone formation.[9-11]

Saturated bile may be produced in the liver, or normal hepatic bile may become saturated in the gallbladder. Current evidence supports the conclusion that the liver is the source of this abnormal bile.[7,8] Cholesterol gallstone formation could therefore be considered a primary hepatic disease. Alternatively, an abnormality of the enterohepatic circulation could induce the liver to secrete saturated bile.[12]

How does the liver produce saturated bile? Normally, cholesterol is insoluble in water but is brought into solution in bile by its molecular association with bile acids and phospholipids. The predominant phospholipid in bile is lecithin. The water-soluble bile acids act as solvents for lecithin and cholesterol in bile, and can incorporate cholesterol-lecithin liquid crystals into molecular aggregates called mixed micelles.[13] These mixed micelles have a finite capacity to dissolve cholesterol. Therefore, the solubility of cholesterol in bile depends primarily on the relative proportions of bile acids, lecithin and cholesterol.

The relative molar proportions of biliary lipids may be plotted on triangular coordinates (Figure 1).[14] Any point within the triangle represents a combination of the three components, expressed in millimols and totaling 100 percent. Any point

below the line of cholesterol saturation has sufficient concentration of bile acids and lecithin to maintain cholesterol in micellar solution. Points on this line represent bile saturated with cholesterol, whereas above the line cholesterol is in a crystalline, liquid crystalline or supersaturated state. Normal bile composition lies within the micellar zone.

Additional methods for determining cholesterol solubility and modifications in the original Admirand and Small line[14] have been proposed (Figure 1).[15] Metzger and associates[16] have defined a lithogenic index. Other workers have determined ratios of the concentration or secretion rates of cholesterol to that of bile acids plus lecithin. The most applicable method to express lithogenicity remains yet to be determined.

The liver might produce saturated bile by either a decreased secretion of the solubilizing lipids (predominantly bile acids, as bile acids stimulate synthesis and secretion of biliary lecithin)[17] or by an increased secretion of cholesterol.[18] The evidence favors a combination of these two mechanisms.

Decreased Secretion of Solubilizing Lipids—Bile Acids

In patients with gallstones[19,20] there is a significantly smaller total, cholic and chenodeoxycholic acid pool than in matched controls without stones. Biliary bile acid secretion has been reported to be decreased or normal in Caucasians with gallstones,[21] despite a decreased bile acid pool.

Why is the bile acid pool decreased in most patients with saturated bile? A defect in hepatic bile acid synthesis has been proposed as one possible explanation. Normally, bile acids are formed in the liver as the major catabolic and excretory products of cholesterol.[22] The initial and rate-limiting step in the formation of bile acids is the 7-α-hydroxylation of cholesterol.[23]

In man, the total bile acid pool is about 2 to 4 grams. Almost all of the hepatic output of bile acids is resorbed actively in the ileum and returned to the liver via the portal vein. The removal of bile acids from the portal blood is virtually complete in one passage through the liver. Inasmuch as this enterohepatic cycling occurs 6 to 8 times a day, 18 to 24 grams of bile acid are secreted daily.[24]

Hepatic bile acid synthesis is controlled by a negative feedback mechanism, whereby the rate of synthesis varies inversely with the rate of return of bile acids to the liver.[25] The enterohepatic circulation of bile acids, therefore, determines the rate of hepatic synthesis and secretion of bile acids. Bile acid synthesis is increased by interruption of the enterohepatic circulation;[26] a 20 percent interruption, however, produces saturated bile in man.[27] A diminished return of bile acids to the liver normally should stimulate hepatic bile acid synthesis. By contrast, the liver of gallstone patients may not be able to increase production in response to this decreased return of bile acids.[28] This defective bile acid synthesis has been attributed to an hepatic enzyme defect. Recently, Nicolau and colleagues[29] measured (and our group has confirmed)[30] the *in vitro* bile acid synthesis rate in the livers of patients with gallstones. Both groups found that hepatic cholesterol 7-α-hydroxylase activity was strikingly reduced. These preliminary data suggest an enzymatic basis for the reduced bile acid pool in patients with gallstones, although a direct relationship between synthesis and pool size or secretion has not been established.

The hypothesis of "inappropriate repression" has been questioned. The size of the bile acid pool and the number of enterohepatic circulations of the pool determine the total amount of bile acids secreted by the liver. Previously, it had been assumed that a low rate of bile acid secretion could be inferred from the existence of a small bile acid pool. Northfield and Hofmann,[31] however, determined that in patients with gallstones small bile acid pools were associated with normal secretion rates—a finding that suggests a high rate of recycling. They found that secretion rates remain constant over a wide range of pool sizes. Because this implies normal bile acid return to the liver, the finding of a normal synthesis rate suggests a normal feedback regulation of bile acid synthesis. Similarly, in cholecystectomized patients with complete interruption of the enterohepatic circulation, bile acid synthesis was four times that of normal or cholecystectomized subjects with an intact circulation.[28,32]

To summarize, certain data suggest that an abnormality of the enterohepatic circulation may be instrumental in inducing the liver to secrete saturated bile.

Increased Secretion of Cholesterol by the Liver

The cholesterol secretion rate in bile is increased in Caucasian women with gallstone dis-

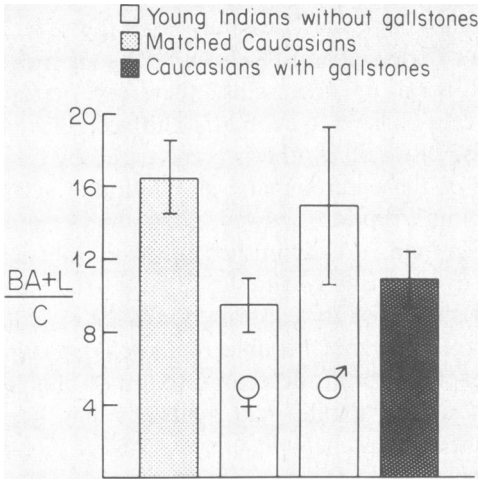

Figure 2.—Ratios (Mean±2 S.E.) of bile acid (BA) plus lecithin (L) to cholesterol (C) designated in the ordinate. These ratios were significantly lower among young Indian women without gallstones than among white controls and Indian men. (Reproduced with permission from *The New England Journal of Medicine.*[36])

ease. Increased cholesterol secretion can result either from excessive cholesterol input or deficient cholesterol conversion into bile acids, or both.[18] Increased hepatic synthesis of cholesterol appears to be responsible for the increased secretion of cholesterol. Nicolau and co-workers[29] found (and again, our group has confirmed)[30] an increased activity of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase, the rate-limiting enzyme for cholesterol synthesis in the liver of gallstone patients.

In summary, a dual defect, that is, an increase in cholesterol synthesis and secretion, and a reduction of bile acid synthesis and secretion, may be the basis for bile saturation. Supersaturation of bile with cholesterol is prerequisite to the precipitation of cholesterol and the subsequent formation and growth of cholesterol gallstones.

- *Crystallization*

In this stage, the excess cholesterol is precipitated from saturated bile. Bile then has two physical states: a solid phase, consisting of cholesterol crystals (or gallstones); and a liquid phase, consisting of bile saturated with cholesterol.

- *Growth*

This final stage begins with the formation of microscopic stones, perhaps by further growth of the crystals originally precipitated. The rate of stone growth is determined by the balance between the rate of precipitation and the rate of dissolution or passage of crystals into the intestinal tract. Gallstones usually grow in the gallbladder, where bile remains for several hours before being emptied into the duodenum. Biliary stasis, the frequency and efficiency of gallbladder emptying, and infection may play a role at this stage.[33]

High-Risk Groups for Cholelithiasis

Specific Populations

American Indians have a high incidence of gallbladder disease.[34] Recent studies document the magnitude of the problem in the Pima Indian population. Gallstones occur in 70 percent of Pima women by age 30, and they develop in 70 percent of Pima men in later life. Gallstones were symptomatic in about half of these subjects. A similar incidence of symptomatic stones has been found among Chippewa women in northern Minnesota.[35] In this population, the ratio of bile acid plus lecithin to cholesterol in duodenal bile in young women without gallstones was significantly lower than in a matched control group of Caucasians, and not different from that found in white women with gallstones (Figure 2).[36]

Heredity

Genealogy studies support the widespread clinical impression that there is a genetic basis for gallstone disease; familial aggregation has been reported frequently. Definite evidence of gallbladder disease was found in the mother or father of 33 of 100 patients in whom operations were carried out on the biliary tract.[37] Definitive or suggestive evidence of gallbladder disease was found in a sibling, parent or the offspring of 72 percent of these patients. Findings in a study of biliary lipid composition in siblings of young patients with gallstones showed a higher incidence of saturated bile (and therefore a greater likelihood of subsequent development of gallstones) than in a matched controlled population.[35] However, a Danish study of twins[38] showed discordance for gallstone disease in monozygotes who were 40 years of age or older, therefore excluding a simple genetic explanation. Dietary and environmental factors may influence genetic predisposition.

Ileal Disease

In patients with disease of terminal ileum or with small bowel resection there is an increased

incidence of cholesterol gallstones.[39,40] This increased incidence of cholesterol gallstones is presumably due to diminished bile acid absorption and pool size and the resultant decrease in biliary cholesterol solubilization. Dowling and colleagues[41] found that nine of ten patients with ileal disease had supersaturated bile.

Miscellaneous

In patients with coronary artery disease, peptic ulcer, vagotomy, gastric retention, cirrhosis, hyperparathyroidism and other clinical disorders[42] there may be an increased incidence of gallstone formation. The exact mechanisms of gallstone formation in these conditions are unclear and deserve further study.

Pregnancy

Gallstones are more common in women who have had children than in nulliparous women, although the degree of parity does not correlate with the prevalence of gallstones. During the progesterone phase of the menstrual cycle and during pregnancy, the humeral mechanism that usually elicits contraction of the gallbladder and relaxation of Oddi's sphincter is impaired.[43] The resultant increase in the stasis may be an important factor superimposed on changes in biliary lipid composition.[44]

Obesity

Gallstones are more common in obese patients than in thin patients or in the general population. Sarles and co-workers[45] in France have shown that patients with gallstones consume significantly more calories than control subjects. Moreover, they reported a significant direct correlation between gallstone formation in man and the concentration of cholesterol in bile, as well as the total calories ingested, regardless of the amount of fat, carbohydrate or protein in the diet.

The synthesis of cholesterol is proportional to the total body weight and, therefore, is increased in obesity. In obese patients who have gallstones, body weight correlates with biliary cholesterol.[46] Weight reduction has been shown to cause a lowering of cholesterol synthesis, and therefore it would seem likely that weight reduction would also decrease hepatic secretion of cholesterol. A recent report[47] indicated that bile composition in obese patients (during a period of weight reduction on a 1,000-calorie-per-day diet) showed a relative increase in lithogenicity in five or ten patients studied in the course of weight reduction. The lithogenicity of bile temporarily becomes worse during weight loss, but once weight is stabilized at a reduced level, bile becomes consistently less saturated.

Medications

Birth Control Pills—Estrogen-Containing Compounds

Two reports from the Boston Collaborative Drug Surveillance Program suggest that women of child-bearing age who used oral contraceptives, or postmenopausal women who had taken estrogen for menopausal symptoms, had an increased risk (2 to 2½ times that of a control group) of having gallbladder disease.[48,49] Pertsemlidis and co-workers[50] showed that patients given oral contraceptives developed an increase of cholesterol concentration in bile, and a decrease of bile acid synthesis rate and pool size. These findings show that contraceptive pills increased the saturation of bile with cholesterol.

Clofibrate

Clofibrate (Atromid-S®) is an inhibitor of cholesterol synthesis. This hypocholesterolemic agent, however, has been reported to increase cholesterol saturation of bile.[51] Furthermore, in another study clofibrate caused an increase of cholesterol concentration in bile and a decrease in the concentration, pool size and synthesis of bile acids.[50] It was not surprising, therefore, that the coronary drug project study of patients receiving long-term dosages of clofibrate found a more than twofold increase in incidence of gallstones in patients treated with clofibrate.[52]

Symptoms

In about 50 percent of patients with cholelithiasis symptoms develop secondary to biliary tract disease. The reason gallstones cause symptoms or complications in one person and not in another remains an enigma.

Two common myths or misconceptions concerning the clinical manifestations of cholelithiasis have been clarified. Fatty food intolerance or other qualitative dyspepsia, eructation, flatulence, aerophagia, pyrosis or other vague epigastric discomforts do not contribute to the diagnosis of cholelithiasis. These associated symptoms are fortuitous and comparably prevalent in about 50 percent of patients without gallstones.[53] Dyspeptic symptoms are nonspecific and not re-

lated to the presence of gallstones; the removal of the gallbladder will not consistently relieve these symptoms.

Biliary colic is the most important symptom in the diagnosis of cholelithiasis. Characteristically, the pain is of sudden onset, often severe and steady, lasting as long as three hours (usually less than one hour in 40 percent of cases). This pain does not increase and decrease in intensity and is not typically "colicky."[54] Therefore, the term biliary colic appears to be a misnomer.

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY (ERCP)

JOEL PANISH, MD:* The technique of ERCP consists of introducing a right-angled viewing fiberoptic duodenoscope into the second portion of the duodenum; visualizing the ampulla of Vater; cannulating the papilla with a small catheter and introducing radiopaque dye into the biliary tree or the pancreatic duct or both.[55-58]

Indications

- *Differential diagnosis of jaundice*—It is no longer necessary to observe a problem jaundice case for weeks in order to decide whether the cause is intrahepatic or extrahepatic. If the customary diagnostic procedures fail, we advocate ERCP early in the course of jaundice.
- *Evaluation of postcholecystectomy syndromes*—The technique is useful when there is suspicion of postoperative stricture, new or retained common bile duct stones or a long cystic duct stump; for example, in patients who have symptoms of recurrent pain, fever, abnormal findings on liver function tests without jaundice, and in patients in whom cholecystectomy has been carried out.
- *Suspected cholelithiasis*—Another use is for evaluation in the small group of patients whose clinical history suggests cholelithiasis (perhaps in whom there have been minimally abnormal findings on liver function tests) and in whom results on oral cholecystogram and intravenous cholangiogram have been normal.
- *Suspected biliary tract disease with a history of allergy to iodine*—In our experience these patients tolerate intraductal injections of dye without adverse reaction.
- *Suspected carcinoma of the pancreas.*
- *Patients with recurrent pancreatitis*—The technique may be used to evaluate for ductal stones, strictures or pseudocyst, and to help formulate the type of surgical approach most feasible for correction of cause of recurrent pancreatitis. The pathologic anatomical findings on pancreatogram help to decide in advance what type of surgical procedure would have the best chance of success in relieving the disease process.
- *Patients diagnosed as having primary biliary cirrhosis*—The technique is useful for ruling out with certainty any extrahepatic biliary block.
- *Endoscopic sphincterotomy and removal of common bile duct stones*—This procedure has been successful as reported in both the Japanese and German literature (with excellent two-year follow-ups).[59,60]

Technique

Contraindications to carrying out the examination are the presence of acute pancreatitis, a positive hepatitis B antigen and acute myocardial infarction within the preceding six weeks.

The patient is fasted overnight; a 5 percent dextrose/water solution is given intravenously in the right arm; the patient is placed in the left lateral position and premedicated to the point of drowsiness with meperidine (Demerol®) or diazepam (Valium®), or both, administered intravenously. The Olympus JF scope is introduced into the stomach and passed under direct vision through the pylorus into the second portion of the duodenum. The patient is then placed in the prone position and the ampulla of Vater is located and an "en face" view is achieved. (If duodenal hypermotility is a problem, 1 mg of glucagon is given intravenously; if it persists, intravenous administration of probanthine may be tried.) A small cannula is then introduced through the scope into the papillary orifice.

The ductal system that the examiner wishes to view is identified by injecting a small amount of 60 percent renografin solution and observing the flow of dye on a fluoroscopic screen. The pancreatic duct is usually outlined with 2 to 10 ml of dye, under gentle pressure. The biliary tree will tolerate 20 to 50 ml of dye. If both ductal systems are not seen, further manipulation of the cannula to gain entrance into the desired duct will have to be carried out. This may entail repositioning the scope or the patient, or both. Once the desired duct is opacified, radiographs are obtained, both with the scope and cannula in place and after they

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are removed. The diagnostic accuracy of the examination depends on the clarity of the radiographs obtained and upon the radiologic equipment used.

Complications

In almost all patients, a postprocedure chemical pancreatitis will develop, with levels of serum amylase rising as high as 300 to 400 units for one

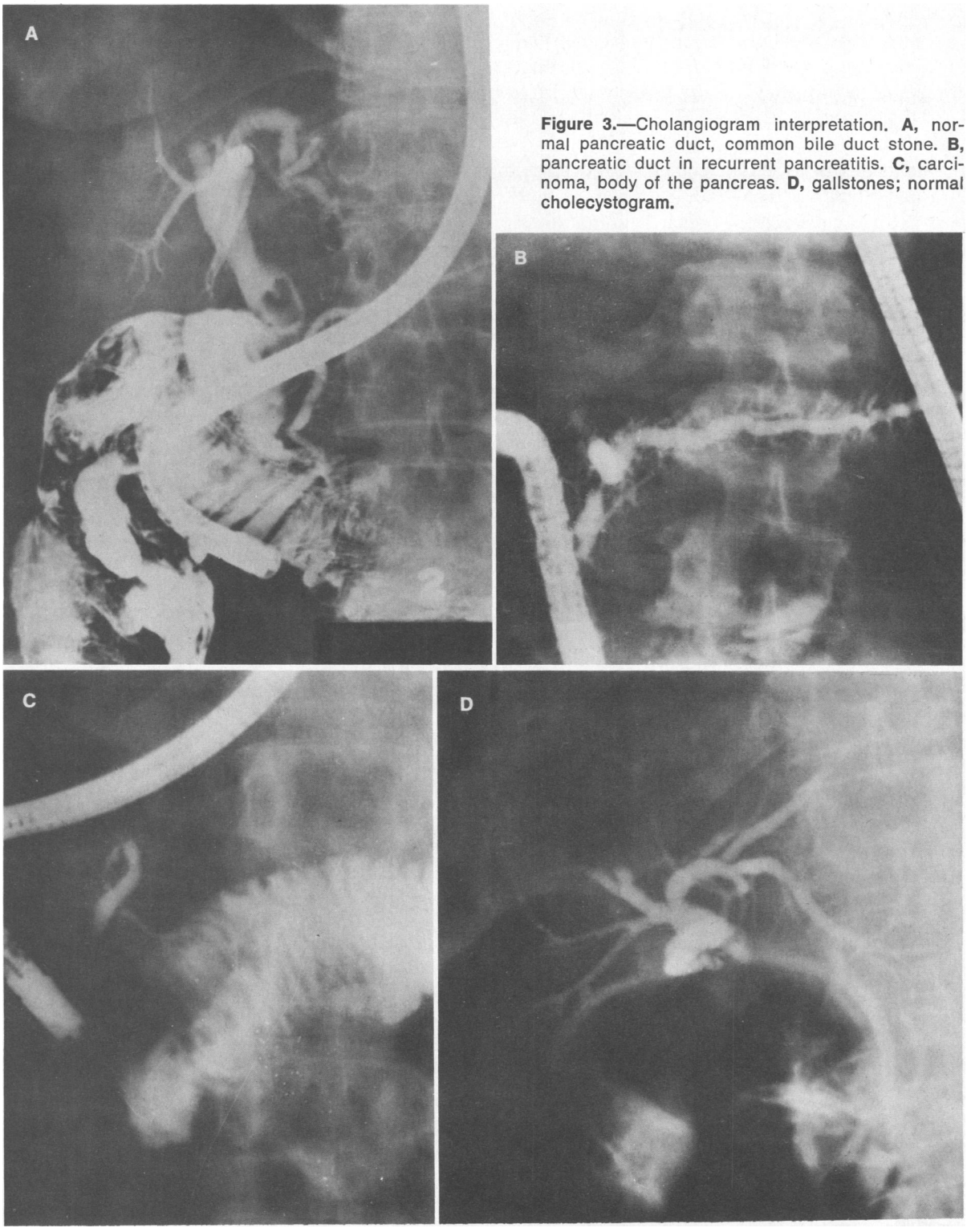

Figure 3.—Cholangiogram interpretation. **A,** normal pancreatic duct, common bile duct stone. **B,** pancreatic duct in recurrent pancreatitis. **C,** carcinoma, body of the pancreas. **D,** gallstones; normal cholecystogram.

to two days. However, in less than 1 percent does there develop clinical pancreatitis with abdominal pain or fever, or both, and these resolve within four to five days. There is a distinct possibility of infection in the presence of a pseudocyst; if a pseudocyst is shown to be present, administration of antibiotics should be started immediately and the patient observed closely. If an infection occurs and is not rapidly alleviated by medical measures, immediate surgical drainage of the pseudocyst is indicated.

The danger of ascending cholangitis developing in a patient with a high-grade extrahepatic block is a definite possibility. If such a lesion is suspected clinically, administration of prophylactic antibiotics should be begun 24 hours before the procedure; should the clinical suspicion be proved radiologically, treatment should be maintained for 48 hours thereafter. If such a lesion is encountered during the examination and the patient has not been receiving antibiotics, drug administration should be started immediately. These measures usually prevent or treat cholangitis successfully, thereby eliminating the necessity for immediate surgical intervention. If cholangitis occurs and is unresponsive to antibiotic therapy within 24 to 48 hours, immediate operation is indicated.

Results

Our current success rate in cannulating and showing the desired duct is about 85 percent; common bile duct, 75 percent, and the main pancreatic duct, 95 percent. The common bile duct is more difficult to cannulate, particularly in the presence of carcinoma of the head of the pancreas. It is possible to cannulate the papilla of Vater after gastric resection with Billroth I or II anastomoses, or in the presence of cholecystoduodenostomy, choledochoduodenostomy, sphincterotomy or sphincteroplasty. The examiner's rate of success is directly proportional to the number of procedures he has previously done.

Results of interpretation of cholangiograms have been excellent (Figure 3). Stones have been discovered in both the gallbladder and common bile duct when findings on cholecystography and intravenous cholangiography were reported as normal. Although there may be significant difficulty in filling the intrahepatic biliary radicles, by placing the patient supine and with the head down, proper filling and interpretation become possible.

The major interpretive difficulty lies in the differential diagnosis of chronic pancreatitis and carcinoma of the pancreas.[61] Similar ductal changes may be present in both diseases. It appears that this difficulty can be resolved with more experience and by utilizing magnification radiologic techniques.

It has not yet been shown whether earlier diagnosis of pancreatic carcinoma is possible, and whether the ultimate survival of the patient with this disease can be improved.

Future

The future appears promising. Electrocautery sphincterotomy with basket removal of common bile duct stones has been safely carried out. Long-term results relating to sphincter stenosis[59] and recurrent stones are not yet available, however.

Opacification of the entire pancreas by means of radiopaque dye enhanced by drugs appears possible. Pressure measurements of the sphincter of Oddi, indicating normal and pathologic effects of various drugs thereon, are being carried out and have therapeutic implications. It is now possible to collect cytological specimens directly from the pancreatic duct; this may aid in the earlier detection of cancer and perhaps influence surgical cure of that disease.

CHOLEDOCHOSCOPY

J. MANNY SHORE, MD:* The recent invention of the "rod-lens" optical system has led to the design of an improved rigid choledochoscope that overcomes limitations of previous biliary endoscopes (Figure 4).[62] This system allows miniaturization, so that the 5 cm exploring horizontal limb—incorporating optical, lighting and irrigating systems—measures only 5 by 3 mm in cross section. The right-angle construction and compact design eliminate difficulties encountered with previous scopes and overcome troublesome manipulation associated with flexible instruments. The wide viewing angle, increased light transmission, excellent resolution, extreme depth of field and infinity focus provide the exquisite image quality so essential for prompt endoscopic orientation. These qualities permit mastery of the endoscopic technique by surgeons after a minimum of training and experience. A standard fiberoptic light source and light transmitting cord and a saline pressure

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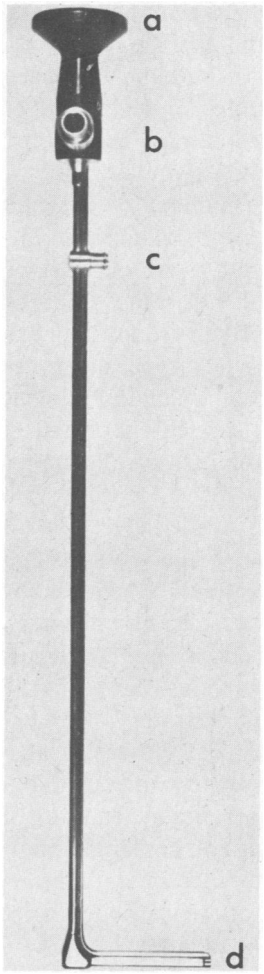

Figure 4.—Right-angled choledochoscope with Hopkins optical system. **a,** viewing eyepiece; **b,** attachment for light cord; **c,** attachment for irrigation; **d,** exploring horizontal limb, 5 cm long and 5 by 3 mm in cross section.

irrigation system complete the apparatus. Continuous irrigation is required to keep the ductal system distended for proper observation. The equipment is gas-sterilized.

Technique

The choledochoscope is introduced through the choledochotomy incision after completion of choledochal exploration. Technical details for assembling and properly utilizing the instrument have been described elsewhere.[63] The entire stone-bearing portion of the biliary system can be visualized, from the ampulla to the tertiary hepatic radicles (Figure 5). Abnormal changes—such as the presence of calculi, cholangitis, neoplasm, diverticula or strictures—can be promptly and accurately identified. Generally, calculi found by endoscopy can be blindly removed by manipulation after withdrawing the scope. When this is not possible, stone-retrieving instruments passed through a separate guide channel attached to the scope can be advanced under visual control. In

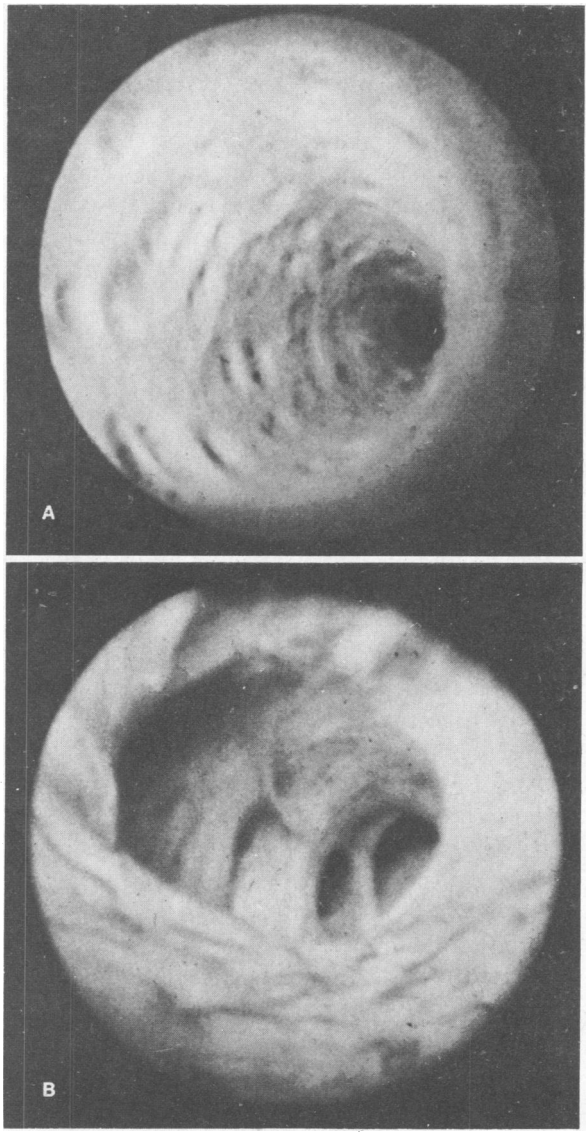

Figure 5.—Endoscopic views of biliary tract. **A,** distal common bile duct and sphincter of Oddi. **B,** hepatic ducts.

rare instances, a calculus visualized by endoscopy defies removal by all available techniques, and is managed by a biliary bypass procedure. When a neoplasm of the biliary tract is identified, it can be precisely biopsied under visual control.

Clinical Experience

A total of 342 patients have had choledochotomy, choledochoscopy and operative cholangiography carried out at the Cedars-Sinai Medical Center between 1960 and 1974 (Table 1). While our experience with the first two endoscopic instruments noted in the table was satisfactory, the vastly improved mechanical and optical qualities

of the present choledochoscope have rendered the others obsolete; superior performance now qualifies this instrument as the definitive biliary endoscope.

Between 1970 and 1974, the new choledochoscope was evaluated in 84 patients in whom primary choledochotomy was carried out and 19 patients in whom secondary exploration was done. In each case biliary endoscopy was done after choledocholithotomy with conventional instrumentation. When overlooked stones were detected, endoscopy was repeated following their removal, until clear ducts were visualized. Completion operative and postoperative T-tube cholangiograms were obtained in all patients.

Results

In 84 primary explorations for stones, no calculi were found in 30 patients. In 53 of 54 patients with calculi the ducts were cleared of all calculi by exploration, endoscopy and cholangiography. In one patient (1 percent) an overlooked stone was found by postoperative T-tube cholangiography. Calculi were also retained in two of 19 patients (10 percent) in whom secondary choledocholithotomy was done.

Biliary endoscopy was helpful to the surgeon in most of the cases, especially in the detection and removal of calculi missed by initial cholangiography and conventional instrumentation. It also facilitated operative management in complex cases by providing precise information by direct visualization. When filling defects or nonpassage of dye into the duodenum were found, biliary endoscopy clarified interpretation of completion operative cholangiograms. The overall result was one of increased efficiency, accuracy and reduction of operating time.

Discussion

While the use of completion operative cholangiography has detected many calculi missed by instrumental exploration, overlooked stones are still detected postoperatively in approximately 10 percent of choledocholithotomies.[64-69] The use of other intraoperative devices, such as the Fogarty biliary catheter[70] and the Eisman ultrasonic probe,[71] has failed to reduce the incidence of missed stones significantly beyond that of cholangiography. Operative biliary endoscopy, however, has consistently been found by investigators[63,72-82] to decrease the number of retained calculi to less than 2 percent of choledocholithotomies. Even fewer stones are overlooked, since stones that are visualized but not removable can be treated definitively by primary duct-drainage procedures. Although the latter type of stones may be retained, their detection by endoscopy has led to prompt corrective surgical procedures, thereby eliminating the probability of symptomatic recurrence.

The precise observation provided by choledochoscopy has been of value in many ways. Removal of missed calculi identified by endoscopy has been facilitated. This has occasionally been possible only under direct endoscopic guidance. The definitive information provided can promptly indicate appropriate operative strategy—for example, the decision to carry out either a transduodenal exploration or a biliary intestinal bypass procedure. The proper interpretation of doubtful or suspicious findings on cholangiograms has on several occasions shortened operating time by eliminating the need for repeat cholangiograms, reexploration or duodenotomy.

The major application of operative biliary endoscopy is in the management of choledocholithiasis. Tumors of the biliary tract can be visualized and biopsy specimens taken, but they are rare. Differentiation of distal duct obstruction due to carcinoma of the head of the pancreas or to chronic pancreatitis is usually not possible by endoscopy.

The technique of biliary endoscopy can be readily learned; the important anatomic landmarks are easily identified. Unlike endoscopic examination of other organs, there is no complex anatomy to master and any abnormalities are quickly recognized. The atraumatic nature of the choledochoscope is shown by the absence of duct

TABLE 1.—*Experience with Biliary Endoscopy, 1960-1974*

Procedure	*Wildegans Scope (Rigid)* 1960-1964	*Fiberoptic Scope (Flexible)* 1965-1970	*Berci-Shore Scope (Rigid)* 1970-1974	*Total*
Primary choledochotomy	54	160	84	298
Secondary choledochotomy	5	20	19	44
TOTAL	59	180	103	342

injury and a low incidence of postoperative complications.

With the introduction of the image amplifier and the "rod-lens" choledochoscope into the armamentarium of the biliary surgeon, a streamlined technique of choledocholithotomy has evolved. The procedure can now be condensed into an efficient stone tracking operation consisting of the following steps:

- *Initial operative cholangiography*—The use of the image amplifier for operative cholangiography eliminates most sources of diagnostic error. Localization of duct pathology before choledochotomy guides subsequent exploration. Documentation of dye passage into the duodenum before operative manipulation eliminates confusion in the interpretation of subsequent films.
- *Guided choledocholithotomy*—Guidance by the initial cholangiogram permits prompt definitive retrieval of demonstrated filling defects by the least traumatic maneuvers. Passage of a Fogarty biliary catheter distally confirms patency and may deliver residual calculi.
- *Choledochoscopy*—Safe and accurate visualization of the stone-bearing portion of the biliary tract is accomplished. Residual stones can be readily seen and retrieved. Conditions that require a concomitant biliary drainage procedure—such as nonremovable calculi or ampullary fibrosis—can be accurately identified.
- *Completion operative cholangiography*—This time-honored step may now be safely eliminated if good-quality initial cholangiograms and biliary endoscopy are routinely done.

Summary

An improved rigid choledochoscope with a "rod-lens" optical system provides rapid, safe and accurate visualization of the biliary tree. Residual stones can be readily seen and retrieved, and biopsy specimens of intraductal neoplasms can be taken under visual control.

In a recent series of 84 patients in whom primary choledochotomy, biliary endoscopy and operative cholangiography were carried out, all calculi were recovered from 53 of 54 ducts containing calculi; a retained stone was found by postoperative cholangiography in one patient (2 percent). The incidence of retained stones has been similarly lowered by all investigators incorporating biliary endoscopy in their armamentarium.

ADVANCES IN OPERATIVE CHOLANGIOGRAPHY

Any assessment of operative cholangiography should begin with a review of current practice. In approximately 60 percent of patients in whom cholecystectomy is done, there is no indication for exploration of the duct. Despite the advice of many investigators that routine cholangiography should be done in such patients,[65-69,83-87] it is frequently omitted and none of these ducts are explored. In the remaining 40 percent of patients, one or more of the indications for choledochotomy is present. In this situation most surgeons today use cholangiography selectively in an attempt to decide which ducts should be opened and which can be apparently left safely alone. When there is a relative indication for exploration and there are negative findings on the operative cholangiogram, the duct is usually not explored; this pertains to approximately 25 percent of cholecystectomies. In the other 15 percent, there is either an absolute indication (such as cholangitis, positive findings on an intravenous cholangiogram, a palpable calculus) or the operative cholangiogram gives positive findings and the duct is explored. Follow-up studies from many centers using the above approach have found that in approximately 4 percent of patients reoperation will be required for common duct stones in the future.[66,87-91] These findings are supported by the Commission on Professional and Hospital Activities. In 1970, 380,000 cholecystectomies were done in this country; during the same time, 19,000 (5 percent) reoperations on the biliary tract, mostly for retained stones, were recorded.

Closer analysis of the sources of error in operative cholangiography can pinpoint specific groups of patients in whom common duct stones are not being detected. Numerous authors* have shown that routine operative cholangiograms will show silent, unsuspected stones in approximately 4 percent of patients. These calculi are overlooked by surgeons who fail to add operative cholangiography to every cholecystectomy. False-negative findings on cholangiograms result from limitations of conventional technique, as well as from errors in interpretation and judgment. A negative finding on an initial cholangiogram in a patient with an indication for choledochotomy creates a dilemma: which one is correct? If the indications

*References 64,66,67,69,83-85,87,92-95

are strictly obeyed, the duct will be explored in far too many cases (40 percent). One of the chief advantages of cholangiography has been a decrease in the number of choledochotomies because of radiologic selection of patients with choledocholithiasis. However, when choledochotomy is circumvented by a negative finding on a cholangiogram, in the face of indications, there is a built-in risk: deliberate choledochotomy in patients under these circumstances has disclosed an error of 10 percent.[64,66,67,86] Completion operative cholangiograms also miss stones in approximately 10 percent of choledocholithotomies, as shown by postoperative T-tube cholangiograms.[64,66,70,87,96]

The overall incidence of stones missed during cholecystectomy is shown in Table 2. It is noteworthy that of approximately 6 percent failures, by far the most (5 percent) occurred in patients in whom the ducts were never opened, either because routine cholangiography was omitted or because negative results on the initial operative cholangiogram precluded choledochotomy in the face of indications. Stones retained following choledocholithotomy constitute a minority. This correlates well with the 4 percent to 5 percent incidence of retained stones that are clinically apparent postoperatively.

Recent technologic advances have afforded an opportunity to enhance the quality of operative cholangiograms and thereby increase their accuracy. The use of a thick-walled catheter that can be easily secured to the cystic duct by a Hemoclip[97] obviates the objections to routine cholangiography based on technical considerations. The incorporation of image amplification, television fluoroscopy and aimed spot films eliminates frequent errors of conventional operative cholangiography due to faulty positioning, timing and exposure. Satisfactory films can be obtained with a portable "C" arm x-ray unit available in most community hospitals. Figure 6 illustrates the more

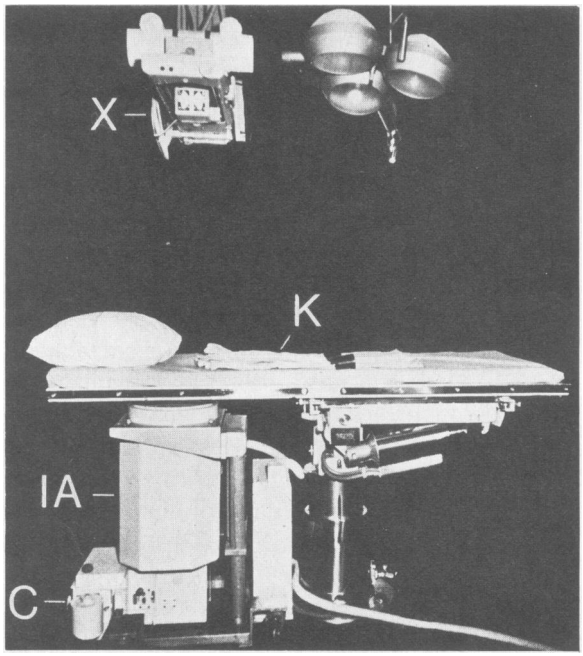

Figure 6.—Equipment for fluoroscopic operative cholangiography. K: Kifa operating table with coordinate radiolucent table top. IA: Mobile image amplifier with beam splitter, television camera and 70 by 70 mm roll film camera (C). X: Overhead x-ray tube. Television monitor is not shown.

versatile equipment currently under evaluation at Cedars-Sinai. A hydraulically controlled Kifa operating table with a radiolucent "floating" table top, permitting movement in two axes for proper positioning, is employed.[98] The ceiling-mounted x-ray tube is aligned with the mobile image amplifier beneath the table. During injection of radiopaque dye, the image is viewed fluoroscopically on a television monitor and can be relayed to a roll film camera for permanent 70 by 70 mm aimed spot films. Image magnification and video recording for instant replay and detailed observation are also available. The filling and emptying phases are observed throughout fluoroscopically, permitting proper timing and positioning of x-ray exposures. Small volume in-

TABLE 2.—*Residual Stones Following Cholecystectomy*

Clinical Group	*Percentage of Cholecystectomy*	*Residual Stones*	
		Percentage of Group	*Percentage of Cholecystectomy*
No indication for choledochotomy			
No cholangiogram, no choledochotomy	60	4	2.4
Indication for choledochotomy			
Cholangiogram negative: No choledochotomy	25	10	2.5
Cholangiogram positive: Choledochotomy	15	10	1.5
TOTAL			6.4

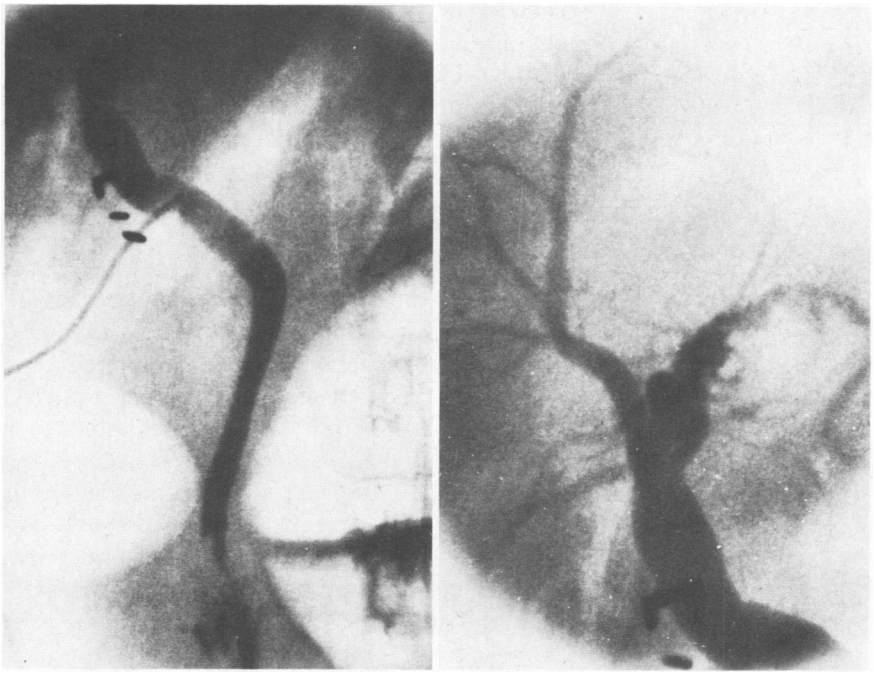

Figure 7.—"Spot" films of operative cholangiograms. **Left,** common bile duct and sphincter. **Right,** hepatic ductal system.

TABLE 3—*Advances in Operative Cholangiography*

Fluoroscopic viewing
Position control
Aimed spot films
Image magnification
Instant replay
Reduced radiation
Functional observation

crements (2 to 5 ml) of 25 percent Hypaque provide optimal visualization in most cases. Observation of rapid emptying into the duodenum signals the need for faster dye injection to fill the hepatic radicles. Proper positioning for spot film exposure of the magnified image (Figure 7) is readily obtained by moving the table top. The dynamic observation of sphincter activity may be useful in evaluating functional biliary disorders. The dry x-ray exposures are available for examination in a special magnifying viewer within minutes. The advantages of fluoroscopic operative cholangiography are summarized in Table 3.

It is anticipated that this approach will eliminate the failures of conventional techniques. Routine cholangiography will detect silent common duct stones and lead to their removal. Fluoroscopic cholangiography will enhance film quality, reducing the incidence of false-negative interpretations. The accuracy of this concept is currently under evaluation in a prospective study at this institution.

MEDICAL DISSOLUTION OF GALLSTONES

DR. SCHOENFIELD: Until recently, surgical operation has been the only definitive treatment for cholelithiasis. Rewbridge[99] in 1937 and Cole and Harridge[100] 20 years later reported the disappearance of gallstone "shadows" by cholangiography in patients treated with mixtures of bile acids. However, only in the past decade, as the understanding of the pathogenesis of cholesterol gallstone formation increased, has a systematic study of medical therapy been undertaken.

Chenodeoxycholic Acid

Danzinger and co-workers[20] showed that chenodeoxycholic acid decreased the cholesterol saturation of bile and dissolved radiolucent gallstones. They administered this bile acid to seven women with asymptomatic radiolucent gallstones visualized by oral cholecystography. In two years, stone size decreased significantly in all patients, with complete dissolution occurring in four. Three subsequent clinical trials[101-103] (two of which were controlled) showed about 60 percent efficacy of chenodeoxycholic acid in dissolving radiolucent gallstones. The rate for spontaneous disappearance of gallstones is less than 1 percent per year; spontaneous disappearance cannot explain the gradual diminution in gallstone size that occurs during therapy with chenodeoxycholic acid. Radiopaque stones have not responded.

The dose of chenodeoxycholic acid in the

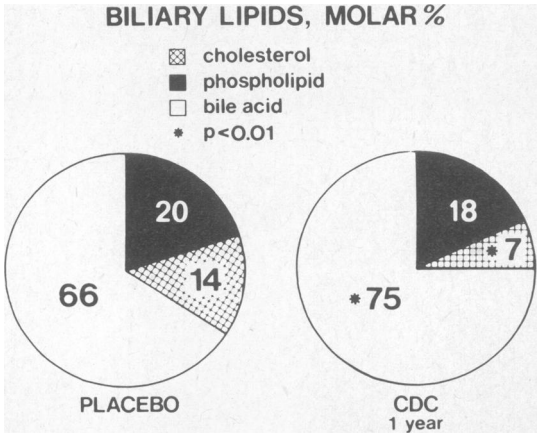

Figure 8.—Composition of biliary lipids in gallstone patients after one year of chenodeoxycholic acid treatment (750 mg per day), expressed as molar percentages of bile acids, phospholipids and cholesterol, totaling 100. In response to therapy, the molar percentage of bile acids increased significantly ($p<0.01$) and the molar percentage of cholesterol decreased significantly ($p<0.01$). (Reprinted with permission from Viewpoints on Digestive Diseases.[104])

therapeutic trials[104] ranged between 750 mg and 4.5 grams daily for 6 to 30 months. The 750 mg dose was as effective as higher doses in decreasing the cholesterol saturation of bile (Figure 8) and causing stone dissolution. Even lower doses of chenodeoxycholic acid (250 to 500 mg) have been found to decrease the saturation of bile, but their ability to dissolve gallstones has not yet been tested.

Within three months after gallstones disappear and treatment is discontinued, bile again becomes saturated with cholesterol. Moreover, recurrence of gallstones has been noted in about 10 percent of patients one year after treatment is discontinued. Accordingly, prophylactic therapy will be necessary at least for some patients after dissolution.

Adverse Reaction

The daily administration of 1 gram or more of chenodeoxycholic acid is often associated with diarrhea. This side effect is the result of the bile acids stimulating the colonic mucosa[105] to secrete water and electrolytes (probably mediated by the cyclic adenosine monophosphate (AMP) system). Lowering the dose to less than 1 gram per day generally obviates this effect.

Thistle and Hoffmann[102] reported that in a third of the patients studied chenodeoxycholic acid was responsible for a twofold transient rise in transaminase, which returned to normal when therapy was continued. Bell and associates[101] observed only minor changes in isocitric dehydrogenase, with no change in transaminase or alkaline phosphatase. Results of liver biopsies of patients receiving chenodeoxycholic acid have shown minor abnormalities in about 20 percent: fatty infiltration in the parenchyma and round cell infiltration in the portal tracts. Coyne and colleagues,[103] however, found this prevalence not significantly different from that reported in untreated patients with gallstones. They concluded that morphologic abnormalities, when found in the livers of patients treated with chenodeoxycholic acid, result from the gallstones rather than from the treatment.

Nevertheless, the effect of chenodeoxycholic acid on the liver in animal studies raises the possibility of hepatotoxicity, which has not been apparent in the limited clinical experience. Webster and co-workers[106] fed chenodeoxycholic acid, 20 mg per kg of body weight, to three rhesus monkeys for four months. The serum transaminase increased in all three and, at autopsy, triaditis was observed in one, with normal hepatic morphology in the other two.

Chenodeoxycholic acid may cause hepatic injury either by a direct action on the liver or indirectly by its bacterial metabolite, lithocholic acid. Coyne and colleagues[103] found in man that the percentage of nonsulfated lithocholic acid in bile increased 360 percent with treatment, whereas Webster and co-workers[106] showed an even greater increase in rhesus monkeys. The effect in humans of chenodeoxycholic acid on the concentrations of sulfated lithocholic acid in the bile and the lithocholic acid in the liver has not been determined. Because sulfation of lithocholic acid has been shown in rats[107] and in humans[108] to enhance its fecal excretion, factors stimulating sulfation may afford protection from increased amounts of lithocholic acid. More investigation is necessary to ascertain how chenodeoxycholic acid administration affects lithocholic acid metabolism and whether this treatment is hepatotoxic in humans.

Although there has been theoretical concern that bile acid therapy might increase the total body pool of cholesterol and thereby increase the risk of atherosclerosis, there has not been an increase in serum lipids in any of the clinical trials. In patients with gallstones, bile acid administration was associated with a decrease in cholesterol pools[109] and with a decrease in the activity of HMG CoA reductase (the rate-limiting enzyme

of hepatic cholesterol synthesis).[30] In addition, two studies reported that bile acid administration was associated with a decrease of serum triglycerides.[110]

Mechanism of Action

In patients with gallstones, chenodeoxycholic acid treatment expands the bile acid pool[20] while decreasing endogenous hepatic bile acid synthesis.[30] Expansion of the bile acid pool results therefore from the exogenous administration of chenodeoxycholic acid. Cholic acid feeding also expands the bile acid pool, but does not cause desaturation of bile or dissolution of gallstones.[102] Chenodeoxycholic acid decreases hepatic cholesterol synthesis[30] and, in contrast to cholic acid, decreases biliary cholesterol secretion.[111] Chenodeoxycholic acid thus exerts its salutory effect on biliary lipids through a dual action of expanding the bile acid pool and decreasing hepatic cholesterol synthesis and secretion (Figure 9).

Gallstone dissolution has required 6 to 30 months of therapy. Desaturation of bile in response to chenodeoxycholic acid occurs rapidly, but the transfer of cholesterol from the stones to the bile is the rate-limiting phenomenon. Slow dissolution or failure occurs particularly with large stones and with those that are radiopaque. Gallstone dissolution is most rapid with pure cholesterol gallstones and is retarded by the presence of compounds that increase the interfacial barrier.

Other Agents

In patients with gallstones, phenobarbital decreases the cholesterol saturation of bile, but less effectively than does chenodeoxycholic acid.[103] Cholesterol crystals disappeared in every case, but no significant decrease in gallstone size was observed. Although the investigators concluded that phenobarbital alone was ineffective in gallstone dissolution, they speculated that this drug might be effective as an adjunct to bile acid therapy or as prophylaxis in patients who are considered to be at high risk. Phenobarbital may exert its salutory effect on biliary lipids by enhancement of hepatic bile acid synthesis and expansion of the bile acid pool.[30,112] In contrast to chenodeoxycholic acid, however, phenobarbital stimulates hepatic cholesterol synthesis;[30] perhaps this explains why this agent is less effective than the bile acid in decreasing biliary cholesterol saturation.

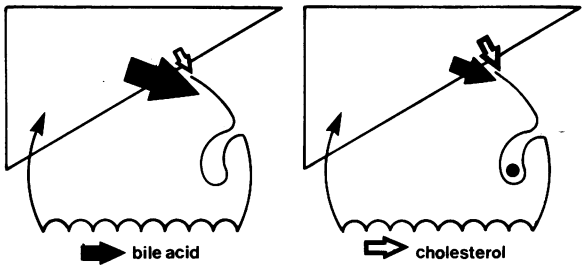

Figure 9.—Diagram of enterohepatic circulation in normal subjects (left) and in patients with gallstones (right). Compared with normal controls, patients with cholesterol gallstones have decreased synthesis and pool size of bile acids, and increased synthesis and secretion of cholesterol. Chenodeoxycholic acid decreases the cholesterol synthesis and secretion, and expands the bile acid pool, rendering bile unsaturated and slowly dissolving gallstones.

Oral administration of lecithin has been proposed as a method to decrease biliary cholesterol saturation. This agent, however, is hydrolyzed in the intestinal tract by pancreatic phospholipase, and only a small amount is reexcreted in the bile. Nevertheless, in one uncontrolled study,[113] oral administration of large doses of lecithin to postcholecystectomy patients with T tubes decreased the cholesterol saturation of bile. Gallstone dissolution, however, has not occurred with lecithin treatment.

Glycerophosphate administration increased biliary phospholipids in rats[114] and decreased biliary cholesterol saturation in nine of ten patients.[115] Further investigation is necessary to determine the safety and efficacy of glycerophosphate treatment for gallstones.

Several therapeutic dietary manipulations have been studied but not yet tested for gallstone dissolution. Bran increases the percentage of chenodeoxycholic acid in the bile and expands the chenodeoxycholic acid pool. A high-fiber diet improves cholesterol solubility in bile. The proportion of unsaturated or saturated fat in the diet, however, did not influence the cholesterol solubilizing capacity of bile.

Future

A simple method for the identification of the prestone state is needed to facilitate population screening. Cholesterol saturation of bile is a prerequisite for gallstone formation, but the ultimate lithogenic phenomena have not been identified. Consequently, a better understanding of the roles of the gallbladder and the enterohepatic circulation in the production of saturated bile and of

cholesterol crystallization and gallstone growth are needed.

Treatment of gallstones with chenodeoxycholic acid has shown the feasibility of medical dissolution, but this therapy is still experimental. Efficacy is virtually certain; safety remains to be shown in a large-scale controlled clinical trial. Investigation will determine whether long-term treatment with this agent is hepatotoxic in humans and whether susceptible patients can be identified prospectively. Also, criteria must be developed to predict individual success or resistance to therapy.

If chenodeoxycholic acid is proved to be effective and safe, appropriate indications for prophylaxis and therapy and the need for treatment after dissolution will have to be determined. Concurrently, other therapeutic or adjuvant agents should be pursued. Finally, a controlled comparison between the results of cholecystectomy and medical dissolution will be required.

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